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Preparation and resolution of 2,2′-dimercapto-6,6′-dimethoxy-1,1′-biphenyl: a C_2-symmetric sulfur building block

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Abstract

The preparation of the title dimercaptan **1** starting from 2,2′-dihydroxy-6,6′-dimethoxy-1,1′-biphenyl **2** is described. Resolution of dimercaptan **1** was performed using (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate as a chiral resolving agent. The procedure affords dimercaptan (+)-**1** and (−)-**1** in 98% ee and 93% ee, respectively. A new and direct intermolecular Ullmann coupling resulting in an improved preparation of diol **2** is also reported.

1. Introduction

Chiral hydroxylated biphenyls with a C_2-symmetry axis have attracted considerable interest because of the biological activity of a number of natural products containing this moiety[1] (i.e. compounds **3** and **4**) and because of their ability to transmit conformational information in stoichiometric and catalytic processes[2] (i.e. ligand **5**). Despite the increasing interest in the preparation of ligands and artificial phenoxy ionophores[3] containing thiol and disulfide groups, examples of the corresponding chiral biphenyl derivatives are extremely rare.[4] The ability of the biphenyl system to transmit conformational information[5] has stimulated us to investigate different sulfur containing chiral derivatives built upon the *ortho*-dimethoxybiphenyl unit.

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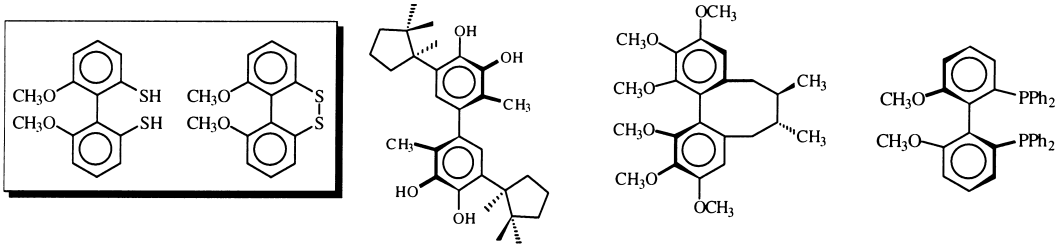
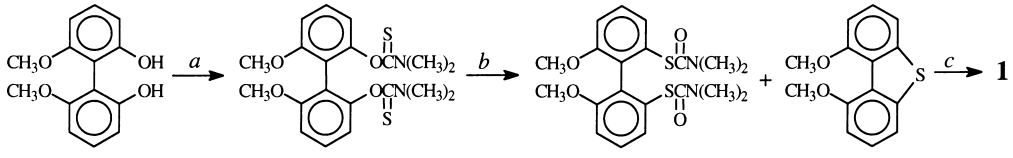


1 **18** (a*S,S,S*)-*aquaticenol*-**3** (a*R*)-*isostegnane*-**4** (a*S*)-MeO-BIPHEP-**5**

Recently we prepared 2,2′-dihydroxy-6,6′-dimethoxy-1,1′-biphenyl **2** both in racemic and enantiomeric form.[6] Since the Newman–Kwart rearrangement of *O*-aryl thiocarbamate to *S*-aryl thiocarbamate followed by reduction with $LiAlH_4$ is a well-known method to achieve the thioaryl derivative,[7] we followed this strategy in order to prepare racemic dithiol **1** (Scheme 1). Pyrolysis of the di-*O*-aryl thiocarbamate **6**, obtained in 80% yield from diol **2** and dimethylthiocarbamoyl chloride, was carried out in a such way as to avoid formation of the monorearranged derivative whereas thiophene **8** was produced in 8% yield. Reduction of di-*S*-aryl thiocarbamate **7** by $LiAlH_4$ in refluxing THF gave dithiol **1** in 54% overall yield. Besides dithiol **1** as the main product of the reaction, we recovered 6,6′-dimethoxy-2-hydroxy-2′-mercapto-1,1′-biphenyl in a very low yield after reduction of pure **7** in the presence of $LiAlH_4$.

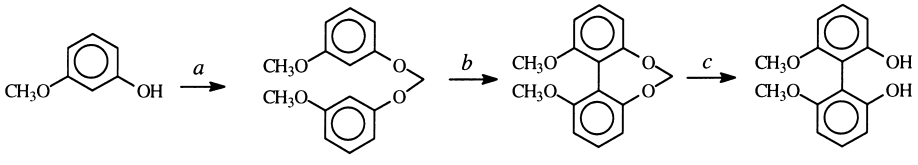


2 **6** **7** **8**

Scheme 1. *a*. $ClC(S)N(CH_3)_2$, NaH, DMF, 85°C, 80% yield. *b*. 285°C, neat, 74% yield. *c*. $LiAlH_4$, THF, 65°C, 90% yield

2. Results and discussion

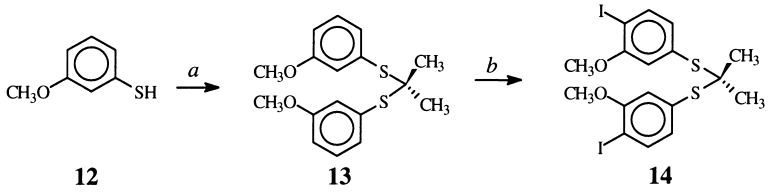
The success of the synthetic strategy for dimercaptan **l** prompted us to improve the method of synthesis of diol **2** with respect to the already published procedures.[6] The method of synthesis is depicted in Scheme 2. Acetal **10**[6] gave the respective biphenyl **11**[6] in 60% yield by treatment with *n*-BuLi at rt and quenching with activated CuI in the presence of pyridine. The route involves generation of the *ortho*-dilithium derivative[8] and treatment of CuI in the presence of a polar, coordinating solvent such as pyridine.[9] Starting from commercial 3-methoxyphenol **9**, biphenol **2** was obtained in 50% overall yield.



9 **10** **11** **2**

Scheme 2. *a*. CH_2I_2, NaH, DMF, 85°C, 88% yield. *b*. *n*-BuLi, Et_2O; CuI, pyridine, 65°C, 61% yield. *c*. 2.2 M CH_3COCl, CH_3OH, rt, 94% yield

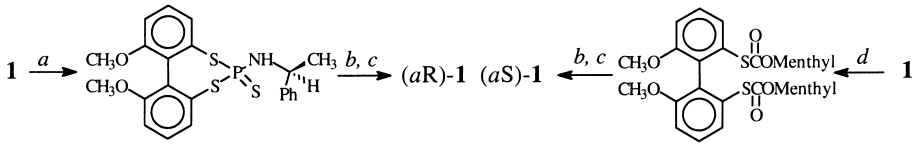
The same procedure applied to the sulfur analogues did not provide the expected product since difficulties were encountered in the formation of the iodo precursor starting from commercial 3-methoxymercaptobenzene **12** as well as its thioacetal derivative **13** (Scheme 3). In particular, the thioacetal **13** in the presence of *t*-BuLi at 0°C after quenching[10] with I_2, gave, besides the starting material, regioisomer **14** as the only product.



12 **13** **14**

Scheme 3. *a*. $(CH_3)_2C(OCH_3)_2$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C; 60% yield. *b*. *t*-BuLi, I_2, Et_2O, −60°C to rt, 70% yield

Several attempts to improve the yield of phosphorothioamidates (a*R*,*S*)-**15** and (a*S*,*S*)-**15** starting from dimercaptan **1** with equimolar (*S*)-α-methylbenzyl dichlorophosphorothioamidate **16** in the presence of pyridine[6] were not successful and a 20% yield of the two diastereomers (1:1) was obtained (Scheme 4). On the other hand, reaction of racemic dithiol **1** with equimolar quantities of (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate in benzene or toluene in the presence of Et_3N at rt gave diastereomers (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**17** and (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**17** in 90% yield.[11]



15 **17**

Scheme 4. *a*. (*S*)-(−)-$Cl_2P(S)NHCH(CH_3)Ph$ (**16**), pyridine, 20% yield. *b*. Separation of diastereomers. *c*. $LiAlH_4$, Et_2O, rt, 88% yield. *d*. (1*R*,2*S*,5*R*)-(−)-Menthyl chloroformate, Et_3N, benzene or toluene, rt, 90% yield

Each diastereomer was readily separated by flash chromatography with 98% and 93% de, respectively.[12] Deprotection of the mercapto group was performed in virtually quantitative yield with $LiAlH_4$ at rt using Et_2O as the solvent. The enantiomeric purity of dimercaptan **1** was calculated by chiral HPLC injecting its disulfide derivative **18** since dithiol **1** did not allow us to obtain sharp chromatographic peaks.[13] Dithiins (a*R*)-**18** and (a*S*)-**18** are optically stable in solution at rt in most solvents and show racemization with a half-time of 1.5 h by warming at 50°C in 2-propanol. No resolution of thiophene **8** was observed after injection on chiral HPLC. This is in accord with the literature for similar compounds.[14]

In conclusion, we prepared a new chiral biphenyl dimercaptan in enantiomeric form. It can be related to the class of C_2-chiral sulfur building blocks to be employed as ligands as well as ionophores. The improved preparation of diol **2** provided a new and direct Ullmann intramolecular coupling. Further studies on the preparation of chiral mercapto biphenyls are in progress.

3. Experimental section

3.1. General procedures

Melting points were determined on a Büchi 530 apparatus and are uncorrected. All ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with a Varian VXR 5000 spectrometer at 299.94

MHz and 75.42 MHz, respectively. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet) or dd (doublet of doublets). Elemental analyses were performed using a Perkin–Elmer model 240 C elemental analyzer. Optical rotations were measured with a Perkin–Elmer 343 spectropolarimeter. The HPLC analyses were performed at rt with a Perkin–Elmer Series 4 liquid chromatograph using a Chiralcel OD column (10 μm, 25 cm×0.46 i.d.) at a flow rate of 0.7 mL/min, 254 UV detection, using a mixture of 98:2 v:v *n*-hexane:2-propanol as the mobile phase. All reactions were conducted under a positive pressure of argon. Tetrahydrofuran (THF), diethyl ether (Et_2O), benzene and toluene were freshly distilled from sodium benzophenone ketyl. Pyridine (py) and triethylamine (Et_3N) were dried over KOH and distilled before use. *N*,*N*-Dimethylformamide (DMF) was dried over 4 Å molecular sieves and distilled before use. All reagents were of commercial quality and used as purchased. Flash chromatography was carried out with silica gel 60 (230–400 mesh, Kiesgel, EM Reagents) eluting with the appropriate solution in the stated v:v proportions. Analytical thin-layer chromatography (TLC) was performed with 0.25 mm thick silica gel plates (Polygram® Sil G/UV_{254}, Macherey–Nagel). The purity of all new compounds was judged to be >98% by ^{1}H NMR and ^{13}C NMR spectral determination.

*3.2. 2,2′-Bis(*N,N-*dimethylthiocarbamoyloxy)-6,6′-dimethoxy-1,1′-biphenyl* ***6***

A solution of diol **2** (3.6 g, 14.6 mmol) in dry DMF (15 mL) was added dropwise to a mixture of NaH (60% oil dispersion) (1.46 g, 36.5 mmol) in dry DMF (15 mL). *N*,*N*-Dimethylthiocarbamoyl chloride (3.95 g, 32.0 mmol) was added in one portion and the reaction mixture was heated at 85°C for 1 h. After cooling, the crude reaction was poured into a 2% solution of KOH (100 mL). The precipitate was filtered, washed thoroughly with H_2O and dissolved in CH_2Cl_2. The organic phase, after drying over Na_2SO_4, gave a solid that was purified by flash chromatography using CH_2Cl_2 as eluent (4.90 g, 80%). Colourless crystals were obtained, mp 132–135°C; ^{1}H NMR δ 2.94 (s, 6H), 3.23 (s, 6H), 3.71 (s, 6H), 6.80 (d, *J*=8.4 Hz, Ar, 2H), 6.96 (d, *J*=8.4 Hz, Ar, 2H), 7.34 (t, *J*=8.4 Hz, Ar, 2H). Anal. calcd for $C_{20}H_{24}N_2O_4S_2$: C, 57.12; H, 5.75; N, 6.66. Found: C, 57.32; H, 5.83; N, 6.40.

*3.3. 2,2′-Bis(*N,N-*dimethylcarbamoylthio)-6,6′-dimethoxy-1,1′-biphenyl* ***7***

A Pyrex tube containing compound **6** (4.90 g, 11.7 mmol) was heated at 285°C for 22 min. After cooling, the crude reaction was dissolved in CH_2Cl_2 and purified by flash chromatography using EtOAc as the eluent (3.62 g, 74%). Compound **7** was obtained as colourless crystals, mp 104–106°C; ^{1}H NMR δ 2.79 (bs, 12H), 3.60 (s, 6H), 6.88 (dd, *J*=1.2, 8.1 Hz, Ar, 2H), 7.19 (dd, *J*=1.2, 8.1 Hz, Ar, 2H), 7.30 (t, *J*=8.1 Hz, Ar, 2H). Anal. calcd for $C_{20}H_{24}N_2O_4S_2$: C, 57.12; H, 5.75; N, 6.66. Found: C, 57.40; H, 5.70; N, 6.51.

*3.4. 1,9-Bis(methoxy)dibenzo[2,1-*b*:1′,2′-*d*]thiophene* ***8***

The compound was obtained as a pale yellow solid in 8% yield from the above reaction, mp 38–40°C; ^{1}H NMR δ 4.02 (s, 6H), 6.96 (dd, *J*=1.5, 7.8 Hz, Ar, 2H), 7.38 (t, *J*=7.8 Hz, Ar, 2H), 7.44 (dd, *J*=1.5, 7.8 Hz, Ar, 2H). Anal. calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 69.01; H, 5.02.

3.5. 2,2′-Dimercapto-6,6′-dimethoxy-1,1′-biphenyl **1**

A solution of **7** (1.34 g, 3.20 mmol) in dry THF (50 mL) was added dropwise to a mixture of $LiAlH_4$ (1.21 g, 31.8 mmol) in dry THF (10 mL) at 0°C. The reaction was heated at 65°C for 7 h. A 5% HCl solution was added cautiously at 0°C and the organic phase was extracted with Et_2O (3×20 mL) and then washed with H_2O (20 mL). The crude reaction mixture was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum as eluent (0.78 g, 88%); mp 125–128°C; ^{1}H NMR δ 3.23 (s, 2H), 3.73 (s, 6H), 6.80 (dd, *J*=0.9, 8.1 Hz, Ar, 2H), 7.04 (dd, *J*=1.2, 8.1 Hz, Ar, 2H), 7.25 (t, *J*=8.1 Hz, Ar, 2H); ^{13}C NMR δ 50.02, 108.32, 121.42, 124.06, 129.31, 133.88, 157.70. Anal. calcd for $C_{14}H_{14}O_2S_2$: C, 60.40; H, 5.07. Found: C, 60.52; H, 5.15.

3.6. 1,10-Bis(methoxy)dibenzo[2,1-d:1′,2′-f][1,3]dioxepine **11**[6]

To a stirred solution of **10** (19 g, 72.90 mmol) in dry Et_2O (250 mL), *n*-BuLi (1.6 M in hexane, 182 mL, 292.0 mmol) was added dropwise. The mixture was stirred under N_2 at 25°C for 48 h. CuI (56 g, 292.0 mmol), dried overnight at 110°C, and pyridine (300 mL) were added at 0°C. The reaction was heated at 65°C to allow the solvent to evaporate. The dark solution was stirred at 65°C for 24 h under N_2. and the product poured into ice, acidified with 10% HCl and triturated with Et_2O (2×100 mL). The organic layer was dried over Na_2SO_4 and rotoevaporated to afford a brown solid. The crude material was purified by flash chromatography on silica gel using a 1:2 mixture of CH_2Cl_2:petroleum as eluent (11.50 g, 61%). ^{1}H NMR δ 3.86 (s, 6H), 5.53 (s, 2H), 6.83 (dd, *J*=0.9, 8.4 Hz, Ar, 2H), 6.89 (dd, *J*=0.9, 8.4 Hz, Ar, 2H), 7.35 (t, *J*=8.4 Hz, Ar, 2H). Anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.64; H, 5.25.

3.7. 2,2′-Bis[3-methoxy-phenylthio]propane **13**

To a solution of **12** (1 g, 7.13 mmol) and 2,2-dimethoxypropane (0.37 g, 3.5 mmol) in CH_2Cl_2 (10 mL), $BF_3 \cdot Et_2O$ (0.88 mL, 7.13 mmol) was added dropwise at 0°C. After stirring for 3 h at 0°C and for 2 h at rt, the reaction was washed with a 5% solution of KOH (100 mL) and then with H_2O (100 mL). The organic phase was dried over Na_2SO_4. After evaporation of the solvent, a colourless oil was obtained (0.68 g, 60%). ^{1}H NMR δ 1.56 (s, 6H), 3.8 (s, 6H), 6.92–6.98 (series of m, Ar, 2H), 7.22–7.28 (series of m, Ar, 6H). Anal. calcd for $C_{17}H_{20}O_2S_2$: C, 63.72; H, 6.29. Found: C, 63.81; H, 6.35.

3.8. 2,2′-Bis[4-iodo-3-methoxy-phenylthio]propane **14**

To a stirred solution of **13** (10.42 g, 32.51 mmol) in dry THF (100 mL), *t*-BuLi (1.7 M in hexane, 48 mL, 81.6 mmol) was added dropwise at −60°C. The mixture was stirred under N_2 at −60°C for 1.5 h. Iodine (20.63 g, 81.29 mmol) was added and the reaction mixture was allowed to warm to rt for 12 h. The solution was diluted with Et_2O, quenched with cold water, dried over Na_2SO_4 and evaporated to give a colourless oil that was purified by flash chromatography on silica gel using a 1:1 mixture of CH_2Cl_2:petroleum ether as eluent (10.14 g, 70%). ^{1}H NMR δ 1.48 (s, 6H), 3.84 (s, 6H), 6.92 (dd, *J*=2.1, 8.1 Hz, Ar, 2H), 7.04 (d, *J*=2.1 Hz, Ar, 2H), 7.69 (d, *J*=8.1 Hz, Ar, 2H). Anal. calcd for $C_{17}H_{18}I_2O_2S_2$: C, 35.68; H, 3.17. Found: C, 36.02; H, 3.06.

3.9. 1,11-Bis(methoxy)-N-(1-phenylethyl)-dibenzo[d,f][1,3,2]dithiophosphepin-6-amine, 6-sulfide **15**

A solution of (*S*)-α-methylbenzylamine (1.2 g, 10 mmol) in dry pyridine (10 mL) was added to a cold solution of thiophosphoryl chloride (1.66 g, 9.8 mmol) in pyridine (10 mL). The reaction mixture was stirred at 0°C for 2 h and 1 h at rt. The heterogeneous mixture was treated with a 5% solution of H_2SO_4 (100 mL) and then with H_2O. The organic phase was extracted with CH_2Cl_2 (3×20mL) to give (*S*)-α-methylbenzyl dichlorophosphorothioamidate **16** (2.36 g, 95%). To a solution of racemic dimercaptan **1** (2.5 g, 9.0 mmol) in pyridine (30 mL) a solution of **16** (2.36 g, 9.28 mmol) was added dropwise at rt. After 4 h of refluxing, the reaction was cooled and treated with a 10% solution of H_2SO_4 (100 mL). After addition of H_2O (100 mL), the organic phase was extracted with CH_2Cl_2 (3×50 mL) to give a solid after evaporation that was purified by flash chromatography using a 1:2 mixture of CH_2Cl_2:petroleum ether as the eluent (1.17 g, 20%). One diastereomer: ^{1}H NMR δ 1.66 (d, *J*=6.6 Hz, 3H), 3.70, (s, 3H), 4.02 (m, 1H), 4.53 (m, 1H), 7.10–7.5 (series of m, Ar, 11H). One diastereomer: ^{1}H NMR δ 1.70 (d, *J*=6.6 Hz, 3H), 3.54, (s, 3H), 4.20 (m, 1H), 4.52 (m, 1H), 7.10–7.5 (series of m, Ar, 11H). Anal. calcd for $C_{22}H_{22}NO_2S_3P$: C, 57.50; H, 4.83; N, 3.05. Found: C, 57.82; H, 4.96; N, 2.92.

3.10. (−)-6,6′-Bis(methoxy)[1,1′-biphenyl]-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methylethyl)-cyclohexyl]-carbothioic ester **17**

A solution of racemic dimercaptan **1** (0.95 g, 3.4 mmol) and Et_3N (2.4 mL, 17.3 mmol) in dry benzene or toluene (20 mL) was added to a solution of (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate (1.78 g, 8.16 mmol) at rt. After 1 h of stirring, the crude reaction was washed with a 10% HCl solution. The organic phase was washed with H_2O (100 mL), dried over Na_2SO_4 and evaporated to give a 1:1 diastereomeric mixture of **1**. Each diastereomer was separated by flash chromatography using a 2:3 mixture of petroleum ether:CH_2Cl_2 as eluent (1.97 g, 90%). One diastereomer, first eluted: 98% de, mp 120–122°C; $[\alpha]_D^{20}$ −0.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 0.71 (d, *J*=7.2 Hz, 6H), 0.83 (d, *J*=7.2 Hz, 6H), 0.85 (d, *J*=7.2 Hz, 6H), 0.8–2.0 (series of m, 18H), 3.67 (s, 6H), 4.67 (m, 2H),), 6.97 (d, *J*=8.1 Hz, Ar, 2H), 7.29 (d, *J*=8.1 Hz, Ar, 2H), 7.37 (t, *J*=8.1 Hz, Ar, 2H); ^{13}C NMR δ 16.28, 20.60, 21.87, 23.34, 26.02, 31.39, 33.98, 40.56, 46.90, 55.74, 77.86, 111.74, 128.09, 129.00, 129.34, 129.92, 157.24, 168.53. Anal. calcd for $C_{36}H_{50}O_6S_2$: C, 67.26; H, 7.84. Found: C, 67.12; H, 8.00.

3.11. (−)-6,6′-Bis(methoxy)[1,1′-biphenyl]-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methylethyl)-cyclohexyl]-carbothioic ester **17**

One diastereomer, second eluted: 93% de, mp 166–169°C; $[\alpha]_D^{20}$ −62.4 (*c* 1, $CHCl_3$); ^{1}H NMR δ 0.70 (d, *J*=7.2 Hz, 6H), 0.81 (d, *J*=7.2 Hz, 6H), 0.84 (d, *J*=7.2 Hz, 6H), 0.8–2.1 (series of m, 18H), 3.68 (s, 6H), 4.65 (m, 2H), 7.00 (d, *J*=8.1 Hz, Ar, 2H), 7.22 (d, *J*=8.1 Hz, Ar, 2H), 7.40 (t, *J*=8.1 Hz, Ar, 2H); ^{13}C NMR δ 16.41, 20.53, 21.89, 23.46, 26.07, 31.29, 33.97, 40.77, 46.95, 55.74, 77.99, 111.78, 128.10, 128.90, 129.45, 129.88, 157.19, 168.61. Anal. calcd for $C_{36}H_{50}O_6S_2$: C, 67.26; H, 7.84. Found: C, 67.16; H, 8.04.

3.12. (+)-2,2′-Dimercapto-6,6′-dimethoxy-1,1′-biphenyl **1**

A solution of **17** (0.26 g, 0.40 mmol) in dry Et_2O (40 mL) was added dropwise to a mixture of $LiAlH_4$ (0.15 g, 4.0 mmol) in dry Et_2O (40 mL) at rt. The reaction was stirred at this temperature for 24 h. A 5% HCl solution was added cautiously at 0°C and the organic phase extracted with Et_2O (3×20 mL) and

then washed with H_2O (20 mL). The menthol was eliminated from the crude reaction by sublimation under vacuum (0.098 g, 88%). From (−)-**17**, first eluted: 98% ee; $[\alpha]_D^{20}$ 26.6 (*c* 1, $CHCl_3$).

*3.13. (−)-2,2′-Dimercapto-6,6′-dimethoxy-1,1′-biphenyl **1***

From (−)-**17**, second eluted: 93% ee; $[\alpha]_D^{20}$ −25.2 (*c* 1, $CHCl_3$).

*3.14. (−)-1,10-Bis(methoxy)dibenzo[2,1-c:1′,2′-e]dithiin **18***

To a stirred 0.2 M solution of mercaptan **1** in CH_2Cl_2 was added iodine at rt until a slight excess of iodine was evidenced by its colour. The reaction was treated with aqueous $Na_2S_2O_3$ and dilute HCl, dried (Na_2SO_4) and evaporated under vacuum to yield 95% of pale yellow crystals after purification by flash chromatography using a 2:3 mixture of petroleum ether:CH_2Cl_2 as eluent. Obtained from (+)-**1**: 98% ee; mp 110–112°C; $[\alpha]_D^{20}$ −118.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 3.84 (s, 6H), 7.00 (m, Ar, 2H), 7.20–7.26 (series of m, Ar, 4H); ^{13}C NMR δ 55.79, 111.09, 121.56, 125.13, 127.74, 142.14, 157.98. Anal. calcd for $C_{14}H_{12}O_2S_2$: C, 60.84; H, 4.38. Found: C, 60.91; H, 4.44.

*3.15. (+)-1,10-Bis(methoxy)dibenzo[2,1-c:1′,2′-e]dithiin **18***

Obtained from (−)-**1** following the above procedure: 93% ee; $[\alpha]_D^{20}$ +112.0 (*c* 0.2, $CHCl_3$).

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13. Racemic disulfide **18** has shown a clear separation with α=1.68 and the ee of each enantiomer **18** was accurately calculated. Racemization measurements were performed by injections of disulfide (−)-**18** at rt several times and then heating with 2-propanol at 50°C until a 50% increase of disulfide (+)-**18** was obtained.
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